UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,403	11/10/2006	Vincenzo Re	PB60550	2439

20462 7590 12/12/2008

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
HOLLOMAN, NANNETTE	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/12/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,403	RE ET AL.	
	Examiner	Art Unit	
	NANNETTE HOLLOMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8-10,12-14,16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-10,12-14,16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Amendment filed on August 18, 2008. All previous rejections have been withdrawn unless stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Specification

The use of the trademark, i.e. GELUCIRE® (p. 7, line 28), has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112 – Enablement (New Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1) Claims 1, 8-10, 12-14, 16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutically acceptable salt of the compound of claim 1 said compound does not reasonably provide enablement for a hydrate of a compound of claim 1. The specification does not provide sufficient guidance nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The nature of the invention

The nature of the invention is a compound of claim 1, or a pharmaceutically acceptable salt of said compound. There is no teaching of hydrates of the compound of claim 1 in the specification.

The state of the prior art and predictability or lack thereof in the art

It is the state of the prior art that it has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compound (See Vippagunta, et al.)

The scope of "hydrate" is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active in vivo. Solvates and hydrates cannot always be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular hydrate or solvate.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what solvates are being included in the elected invention.

The breadth of the claims

The breadth of the claims is a compound of claim 1 or a pharmaceutically acceptable salt or hydrate thereof.

The quantity of experimentation needed and the level of the skill in the art

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents without any direction as to what compounds form hydrates.

To overcome this objection, Applicant should submit an amendment deleting the term "hydrate"

2) Claims 1, 8-10, 12-14, 16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case:

The state of the prior art, state and predictability or lack thereof in the art, and relative skill level

The nature of the invention is a compound of claim 1 comprising a stable polymorphic form of a macrogol glyceride. The relative skill of those in the art is high, that of an MD or PHD. The factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Vippagunta et al., which disclose polymorphs differ in crystal packing and there are usually significant differences in their physical properties, such as density, hardness, melting point, solubility, dissolution rate, and other thermodynamic and kinetic properties.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what polymorphs are being included in the elected invention.

The breadth of the claims

The breadth of the claims is a "polymorphic form" of a macrogol glyceride.

The quantity of experimentation needed

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used in all possible "polymorphic forms" as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 112 – Enablement (Previous Rejection)

Claim 14 was rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes mellitus, does not reasonably provide enablement for treatment and prophylaxis of the diseases broadly claimed. The rejection is maintained.

Applicant's Arguments

Applicant amended claim 14 to recite treatment and/or prophylaxis of diabetes mellitus and metabolic syndrome. Applicant further provided a clinical trial report that the claimed compound is effective at improving mentation in patients with Alzheimer's disease, treating hyperglycemia, and delaying the onset of Type 2 diabetes. These arguments are not persuasive.

Examiner's Response

In regards to the clinical trial report, there is no evidence to the fact of "preventing" any of the claimed diseases. While the compound may improve mentation in patients with Alzheimer's disease, treat hyperglycemia, and delay the onset of Type 2 diabetes, the patients are not "prevented" from the onset of the diseases.

Claim Rejections - 35 USC § 103 (New Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1, 8-10, 12-13, 16 and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (US Patent No. 6,294,192, previously disclosed) and further in view of Sutananta et al. (International journal of Pharmaceutics, Vol. 111, 1994, pp. 51-62).

Patel et al. disclose a capsule for oral administration containing a composition of a hydrophobic therapeutic agent, and a carrier of at least one hydrophilic surfactant and at least one hydrophobic surfactant having an HLB value of less that about 10 (claim 1). Patel et al. further disclose said hydrophobic therapeutic agent is rosiglitazone, which is the compound claimed (col. 22, line 53). Patel et al. disclose preparation of a formulation of a hydrophilic surfactant and a hydrophobic surfactant by heating and adding a therapeutic agent (cols. 31 and 32, example 1). Patel et al. discloses the surfactant is a mixture of a reaction of a polyethylene glycol and a hydrogenated vegetable oil where the product results from transesterification (col. 51, claims 26-

28). Patel et al. also discloses the use of a macrogol glyceride (table 5). It is well known in the art that hydrogenated palm oil as claimed is a hydrogenated vegetable oil.

Patel et al. does not disclose a stable polymorphic form of a macrogol glyceride or any method of preparing the same.

Sutananta et al. disclose the effects of ageing on the thermal behavior and mechanical properties of pharmaceutical glycerides. Sutananta et al. disclose tempering the glyceride materials; i.e. Gelucires, at elevated temperatures resulted in alterations in the distribution of endotherms and represents a possible method of accelerating the transition to the equilibrium form (Abstract). Sutananta et al. disclose the mechanism responsible for ageing affects may be attributed to the conversion of the triglycerides to more stable polymorphic forms (p. 52, col. 1, lines 9-10 and 22-25). Sutananta et al. disclose the method of forming molten tablets of gelucires and allowing the tablets to cool (p. 53, 2nd col., lines 1-10). Sutananta et al. further disclose a method of annealing or tempering the glyceride material at 29 or 36°C for 1-3 days (p. 54, col. 1, line 1). Sutananta et al. disclose the tempering temperature relates to the structure converting to the stable form (p. 55, lines 1-5).

It would have been obvious to one of ordinary skill in the art to use the polymorphic forms of macrogol glyceride in the composition of Patel et al. motivated by the desire to use a more stable glyceride with better mechanical strength in the compositions as disclosed by Sutananta et al. (p.62, line 2).

In regard to the method of claims 16 and 19-22 where the temperature is maintained at 40°C, for 16-72 hrs, is considered to constitute optimization and are

within the scope and skill of an artisan skilled in the art by routine experimentation. See MPEP 2144.05.

2) Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. in view of Sutananta et al. as applied to claims 1, 8-10, 12-13, 16 and 19-22 above, and further in view of Hindley et al. (US Patent No. 6,288,095 B1).

Patel et al. in view of Sutananta et al. do not disclose treatment of diabetes mellitus.

Hindley et al. the use of 5-[4-[2-(N-methyl-N-(2 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione for the treatment of diabetes in a human or non-human, which is the same compound as claimed (column 40, claim 1). Hindley et al. disclose the compound has improved blood-glucose lowering activity (col. 1, line 25).

It would have been obvious to one of ordinary skill in the art to use the composition formulation of Patel et al. in view of Sutananta et al. to treat diabetes in a human motivated by the desire to have a composition that has improved blood-glucose lowering activity as disclosed by Hindley et al.

3) Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. in view of Sutananta et al. as applied to claims 1, 8-10, 12-13, 16 and 19-22 above, and further in view of Matsui et al. (US Patent No. 6,087,384).

Patel et al. in view of Sutananta et al. do not disclose treatment of Alzheimer's disease.

Matsui et al. disclose a method of inhibiting apotosis and treating diseases mediated by promotion of apotosis in a mammal in need (claims 1 and 2). Matsui et al. further disclose using rosiglitazone to treat Alzheimer's disease (claims 11 and 14). Matsui et al. disclose the apoptosis inhibitor of the invention shows and excellent apoptosis inhibitory activity, and is useful as an agent to treat diseases including Alzheimer's disease (col. 15, lines 34-35 and claim14).

It would have been obvious to one of ordinary skill in the art to use the composition formulation of Patel et al. in view of Sutananta et al. to treat Alzheimer's disease motivated by the desire to have a composition that has excellent apotosis inhibitory activity as disclosed by Matsui et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANNETTE HOLLOMAN whose telephone number is (571) 270-5231. The examiner can normally be reached on Mon-Fri 800am-500pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. H./
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612